

SGC Receives \$4.6 Million For Development of Chemical Probes to Epigenetic Targets.

The Ontario Research Fund has announced a 4.6 million dollar investment in a new initiative for the pre-competitive development of 12 chemical probes (small drug-like molecules that can bind to and alter the activity of their target proteins) to study the role of proteins involved in epigenetic signaling.

A selective and potent chemical probe that inhibits a specific protein in a cell is a powerful tool to unravel the protein's role in cellular biology and to assess its suitability as a pharmaceutical target. However, potent, selective, and cell-permeable chemical probes are not widely available because industry increasingly depends on academia to identify and validate cell protein targets while academia depends on industry for the chemical probes it needs to do this work.

The current initiative is a public-private partnership to be led by the Structural Genomics Consortium (SGC) and involves GlaxoSmithKline (GSK) and the National Institutes of Health Chemical Genomics Center (NCGC). This initiative is unique in that industry medicinal chemistry will be applied to an important problem in academia and the resulting chemical probes will be released into the public domain with no restrictions on use. A parallel effort has recently been announced by the Wellcome Trust involving the SGC Oxford, GSK, NCGC and the Departments of Chemistry and Biochemistry at the University of Oxford. Together these projects will produce 37 chemical probes directed against members of each major family of epigenetic targets.

The field of epigenetics studies heritable changes in gene expression that are not due to alterations in DNA sequence. Epigenetic mechanisms are involved in many biological processes including cancer, stem cell biology, inflammation and mental illness. Chemical modifications of chromatin (including DNA methylation and post translational modifications of histones such as methylation, acetylation, and phosphorylation) carry epigenetic information that affects chromatin structure and activity with resultant changes in gene expression. The current initiative will target the major "readers", "writers" and "erasers" of epigenetic marks in the human genome for production of chemical probes. Structural studies at the SGC and elsewhere indicate that these protein families are druggable as they contain defined "pockets" on their molecular surface that could accommodate small drug-like molecules. Chemical probes to these target molecules will be optimized for potency, target selectivity and cellular activity. Information on these chemical probes will be published and deposited in public databases without restriction on their use, and will be made available to Canadian and International scientists through distributors such as Sigma/Aldrich.

"Well characterized chemical probes are hugely useful for target validation and exploration of biology," said Dr. Patrick Vallance, senior vice-president of Drug Discovery at GSK. "This link between the academic community and GSK in an emerging area of science should enhance knowledge and ultimately support our efforts to develop more medicines of benefit to patients."

The NCGC, led by its director, Dr. Christopher Austin, will make several contributions to the project, from assay development to high-throughput screening and medicinal chemistry.

Dr. Peter Brown, SGC Epigenetics Project Manager, is excited about the prospects for this emerging research, “the chemical tools discovered during the course of this project will help unravel the intricacies of epigenetic signaling, and identify those targets with high therapeutic potential.”